John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

ATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAG
TGCTGCCTGCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCG
CAGCGGCCTGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGA
GACCGACGAAGAGCCCGAGGAGCCCGGCCGGAGGGGCAGCTTTGT
GGAGATGGTGGACAACCTGAGGGGCAAGTCGGGGCAGGGCTACTAC
GTGGAGATGACCGTGGGCAGCCCCCCGCAGACGCTCAACATCCTGG
TGGATACAGGCAGCAGTAACTTTGCAGTGGGTGCTGCCCCCCACCC
CTTCCTGCATCGCTACTACCAGAGGCAGCTGTCCAGCACATACCGGG
ACCTCCGGAAGGGTGTGTATGTGCCCTACACCCAGGGCAAGTGGGA
AGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCCATGGCCCCAAC
GTCACTGTGCGTGCCAACATTGCTGCCATCACTGAATCAGACAAGTT
CTTCATCAACGGCTCCAACTGGGAAGGCATCCTGGGGCTGGCCTATG
CTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCT
CTGGTAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTG
TGGTGCTGGCTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCG
GAGGGAGCATGATCATTGGAGGTATCGACCACTCGCTGTACACAGGC
AGTCTCTGGTATACACCCATCCGGCGGGAGTGGTATTATGAGGTGAT
CATTGTGCGGGTGGAGATCAATGGACAGGATCTGAAAATGGACTGCA
AGGAGTACAACTATGACAAGAGCATTGTGGACAGTGGCACCACCAAC
CTTCGTTTGCCCAAGAAAGTGTTTGAAGCTGCAGTCAAATCCATCAAG
GCAGCCTCCTCCACGGAGAAGTTCCCTGATGGTTTCTGGCTAGGAGA
GCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGGAACATTTTCC
CAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTTCC
GCATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTG
GCCACGTCCCAAGACGACTGTTACAAGTTTGCCATCTCACAGTCATC
CACGGGCACTGTTATGGGAGCTGTTATCATGGAGGGCTTCTACGTTG
TCTTTGATCGGGCCCGAAAACGAATTGGCTTTGCTGTCAGCGCTTGC
CATGTGCACGATGAGTTCAGGACGGCAGCGGTGGAAGGCCCTTTTG
TCACCTTGGACATGGAAGACTGTGGCTACAACATTCCACAGACAGAT
GAGTCAACCCTCATGACCATAGCCTATGTCATGGCTGCCATCTGCGC
CCTCTTCATGCTGCCACTCTGCCTCATGGTGTGTCAGTGGCGCTGCC
TCCGCTGCCTGCGCCAGCAGCATGATGACTTTGCTGATGACATCTCC
CTGCTGAAG

FIG. 1A

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

CCATGCCGGCCCCTCACAGCCCCGCCGGGAGCCCGAGCCCGCTGCCCAGG
CTGGCCGCCGCSGTGCCGATGTAGCGGGCTCCGGATCCCAGCCTCTCCCCT
GCTCCCGTGCTCTGCGGATCTCCCCTGACCGCTCTCCACAGCCCGGACCCG
GGGGCTGGCCCAGGGCCCTGCAGGCCCTGGCGTCCTGATGCCCCCAAGCT
CCCTCTCCTGAGAAGCCACCAGCACCACCCAGACTTGGGGGCAGGCGCCA
GGGACGGACGTGGGCCAGTGCGAGCCCAGAGGGCCCGAAGGCCGGGGCC
CACCATGGCCCAAGCCCTGCCCTGGCTCCTGCTGTGGATGGGCGCGGGAG
TGCTGCCTGCCCACGGCACCCAGCACGGCATCCGGCTGCCCCTGCGCAGC
GGCCTGGGGGGCGCCCCCCTGGGGCTGCGGCTGCCCCGGGAGACCGACG
AAGAGCCCGAGGAGCCCGGCCGGAGGGGCAGCTTTGTGGAGATGGTGGAC
AACCTGAGGGGCAAGTCGGGGCAGGGCTACTACGTGGAGATGACCGTGGG
CAGCCCCCCGCAGACGCTCAACATCCTGGTGGATACAGGCAGCAGTAACTT
TGCAGTGGGTGCTGCCCCCCACCCCTTCCTGCATCGCTACTACCAGAGGCA
GCTGTCCAGCACATACCGGGACCTCCGGAAGGGTGTGTATGTGCCCTACAC
CCAGGGCAAGTGGGAAGGGGAGCTGGGCACCGACCTGGTAAGCATCCCCC
ATGGCCCCAACGTCACTGTGCGTGCCAACATTGCTGCCATCACTGAATCAGA
CAAGTTCTTCATCAACGGCTCCAACTGGGAAGGCATCCTGGGGCTGGCCTAT
GCTGAGATTGCCAGGCCTGACGACTCCCTGGAGCCTTTCTTTGACTCTCTGG
TAAAGCAGACCCACGTTCCCAACCTCTTCTCCCTGCAGCTTTGTGGTGCTGG
CTTCCCCCTCAACCAGTCTGAAGTGCTGGCCTCTGTCGGAGGGAGCATGAT
CATTGGAGGTATCGACCACTCGCTGTACACAGGCAGTCTCTGGTATACACCC
ATCCGGCGGGAGTGGTATTATGAGGTGATCATTGTGCGGGTGGAGATCAAT
GGACAGGATCTGAAAATGGACTGCAAGGAGTACAACTATGACAAGAGCATTG
TGGACAGTGGCACCACCAACCTTCGTTTGCCCAAGAAAGTGTTTGAAGCTGC
AGTCAAATCCATCAAGGCAGCCTCCTCCACGGAGAAGTTCCCTGATGGTTTC
TGGCTAGGAGAGCAGCTGGTGTGCTGGCAAGCAGGCACCACCCCTTGGAAC
ATTTTCCCAGTCATCTCACTCTACCTAATGGGTGAGGTTACCAACCAGTCCTT
CCGCATCACCATCCTTCCGCAGCAATACCTGCGGCCAGTGGAAGATGTGGC
CACGTCCCAAGACGACTGTTACAAGTTTGCCATCTCACAGTCATCCACGGGC
ACTGTTATGGGAGCTGTTATCATGGAGGGCTTCTACGTTGTCTTTGATCGGG
CCCGAAAACGAATTGGCTTTGCTGTCAGCGCTTGCCATGTGCACGATGAGTT
CAGGACGGCAGCGGTGGAAGGCCCTTTTGTCACCTTGGACATGGAAGACTG
TGGCTACAACATTCCACAGACAGATGAGTCAACCCTCATGACCATAGCCTAT
GTCATGGCTGCCATCTGCGCCCTCTTCATGCTGCCACTCTGCCTCATGGTGT
GTCAGTGGCGCTGCCTCCGCTGCCTGCGCCAGCAGCATGATGACTTTGCTG
ATGACATCTCCCTGCTGAAGTGAGGAGGCCCATGGGCAGAAGATAGAGATT
CCCCTGGACCACACCTCCGTGGTTCACTTTGGTCACAAGTAGGAGACACAGA
TGGCACCTGTGGCCAGAGCACCTCAGGACCCTCCCCACCCACCAAATGCCT
CTGCCTTGATGGAGAAGGAAAAGGCTGGCAAGGTGGGTTCCAGGGACTGTA
CCTGTAGGAAACAGAAAAGAGAAGAAAGAAGCACTCTGCTGGCGGGAATAC
TCTTGGTCACCTCAAATTTAAGTCGGGAAATTCTGCTGCTTGAAACTTCAGCC
CTGAACCTTTGTCCACCATTCCTTTAAATTCTCCAACCCAAAGTATTCTTCTTT
TCTTAGTTTCAGAAGTACTGGCATCACACGCAGGTTACCTTGGCGTGTGTCC
CTGTGGTACCCTGGCAGAGAAGAGACCAAGCTTGTTTCCCTGCTGGCCAAA
GTCAGTAGGAGAGGATGCACAGTTTGCTATTTGCTTTAGAGACAGGGACTGT
ATAAACAAGCCTAACATTGGTGCAAAGATTGCCTCTTGAATT

FIG. 1B

3/48

MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLGLRL
PRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPP
QTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVY
VPYTQGKWEGELGTDLVSIPHGPNVTVRANIAAITESDKFFINGS
NWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAG
FPLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIV
RVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIK
AASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTN
QSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIM
EGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLR
QQHDDFADDISLLK

FIG. 2A

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

ETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPPQT
LNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVP
YTQGKWEGELGTDLVSIPHGPNVTVRANIAAITESDKFFINGSNW
EGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGFP
LNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRV
EINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAA
SSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQ
SFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQWRCLRCLR
QQHDDFADDISLLK

FIG. 2B

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"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
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MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLGLRL
PRETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPP
QTLNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVY
VPYTQGKWEGELGTDLVSIPHGPNVTVRANIAAITESDKFFINGS
NWEGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAG
FPLNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIV
RVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIK
AASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTN
QSFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIM
EGFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDEDYKDDDDK

FIG. 3A

ETDEEPEEPGRRGSFVEMVDNLRGKSGQGYYVEMTVGSPPQT
LNILVDTGSSNFAVGAAPHPFLHRYYQRQLSSTYRDLRKGVYVP
YTQGKWEGELGTDLVSIPHGPNVTVRANIAAITESDKFFINGSNW
EGILGLAYAEIARPDDSLEPFFDSLVKQTHVPNLFSLQLCGAGFP
LNQSEVLASVGGSMIIGGIDHSLYTGSLWYTPIRREWYYEVIIVRV
EINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKVFEAAVKSIKAA
SSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQ
SFRITILPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIME
GFYVVFDRARKRIGFAVSACHVHDEFRTAAVEGPFVTLDMEDC
GYNIPQTDEDYKDDDDK

FIG. 3B

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
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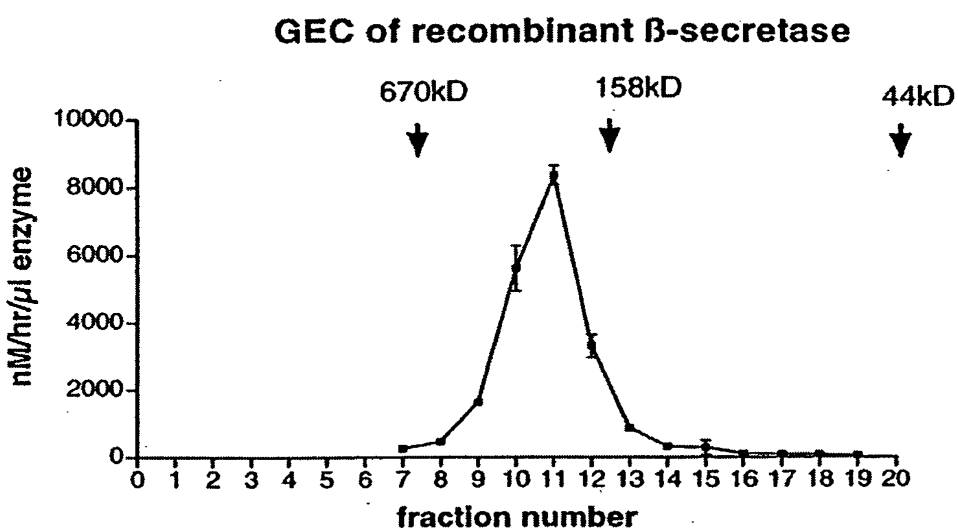

FIG. 4

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
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7/48

Fig. 5A

```
atg gcc caa gcc ctg ccc tgg ctc ctg ctg tgg atg ggc gcg gga gtg    48
Met Ala Gln Ala Leu Pro Trp Leu Leu Leu Trp Met Gly Ala Gly Val
 1               5                  10                  15
[                        Signal peptide                        ]

ctg cct gcc cac ggc acc cag cac ggc atc cgg ctg ccc ctg cgc agc    96
Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu Arg Ser
            20                  25                  30
Signal peptide  >  [                pro region                 ]

ggc ctg ggg ggc gcc ccc ctg ggg ctg cgg ctg ccc cgg gag acc gac   144
Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu Thr Asp
         35                  40                  45
               pro region                   >  [ N term seq ]

gaa gag ccc gag gag ccc ggc cgg agg ggc agc ttt gtg gag atg gtg   192
Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu Met Val
     50                  55                  60
[                     N terminal sequence                      ]

gac aac ctg agg ggc aag tcg ggg cag ggc tac tac gtg gag atg acc   240
Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu Met Thr
 65                  70                  75                  80
[N terminal sequence]

gtg ggc agc ccc ccg cag acg ctc aac atc ctg gtg gat aca ggc agc   288
Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr Gly Ser
                 85                  90                  95
                                                <  Active-D  >

agt aac ttt gca gtg ggt gct gcc ccc cac ccc ttc ctg cat cgc tac   336
Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His Arg Tyr
            100                 105                 110
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Fig. 5B

```
tac cag agg cag ctg tcc agc aca tac cgg gac ctc cgg aag ggt gtg    384
Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val
        115                 120                 125

tat gtg ccc tac acc cag ggc aag tgg gaa ggg gag ctg ggc acc gac    432
Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp
    130                 135                 140

ctg gta agc atc ccc cat ggc ccc aac gtc act gtg cgt gcc aac att    480
Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile
145                 150                 155                 160
                                N-glycos

gct gcc atc act gaa tca gac aag ttc ttc atc aac ggc tcc aac tgg    528
Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp
                165                 170                 175
                                           N-glycos

gaa ggc atc ctg ggg ctg gcc tat gct gag att gcc agg cct gac gac    576
Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp
            180                 185                 190

tcc ctg gag cct ttc ttt gac tct ctg gta aag cag acc cac gtt ccc    624
Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro
        195                 200                 205

aac ctc ttc tcc ctg cag ctt tgt ggt gct ggc ttc ccc ctc aac cag    672
Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln
    210                 215                 220
                                                        N-glycos
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Fig. 5C

```
tct gaa gtg ctg gcc tct gtc gga ggg agc atg atc att gga ggt atc   720
Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile
225                 230                 235                 240
N-gly

gac cac tcg ctg tac aca ggc agt ctc tgg tat aca ccc atc cgg cgg   768
Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg
                245                 250                 255

gag tgg tat tat gag gtg atc att gtg cgg gtg gag atc aat gga cag   816
Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln
            260                 265                 270

gat ctg aaa atg gac tgc aag gag tac aac tat gac aag agc att gtg   864
Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val
        275                 280                 285

gac agt ggc acc acc aac ctt cgt ttg ccc aag aaa gtg ttt gaa gct   912
Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala
    290                 295                 300
    Active-D
gca gtc aaa tcc atc aag gca gcc tcc tcc acg gag aag ttc cct gat   960
Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp
305                 310                 315                 320

ggt ttc tgg cta gga gag cag ctg gtg tgc tgg caa gca ggc acc acc   1008
Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr
                325                 330                 335
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Fig. 5D

```
cct tgg aac att ttc cca gtc atc tca ctc tac cta atg ggt gag gtt   1056
Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val
            340                 345                 350

acc aac cag tcc ttc cgc atc acc atc ctt ccg cag caa tac ctg cgg   1104
Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg
        355                 360                 365

    N-glycos
cca gtg gaa gat gtg gcc acg tcc caa gac gac tgt tac aag ttt gcc   1152
Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala
    370                 375                 380

atc tca cag tca tcc acg ggc act gtt atg gga gct gtt atc atg gag   1200
Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu
385                 390                 395                 400

ggc ttc tac gtt gtc ttt gat cgg gcc cga aaa cga att ggc ttt gct   1248
Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala
                405                 410                 415

gtc agc gct tgc cat gtg cac gat gag ttc agg acg gca gcg gtg gaa   1296
Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu
            420                 425                 430
```

Internal peptide sequence

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Fig. 5E

```
ggc cct ttt gtc acc ttg gac atg gaa gac tgt ggc tac aac att cca   1344
Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn Ile Pro
        435                 440                 445

cag aca gat gag tca acc ctc atg acc ata gcc tat gtc atg gct gcc   1392
Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met Ala Ala
    450                 455                 460

                            Transmembrane
atc tgc gcc ctc ttc atg ctg cca ctc tgc ctc atg gtg tgt cag tgg   1440
Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys Gln Trp
465                 470                 475                 480
                  Transmembrane
cgc tgc ctc cgc tgc ctg cgc cag cag cat gat gac ttt gct gat gac   1488
Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala Asp Asp
            485                 490                 495

atc tcc ctg ctg aag tga                                           1506
Ile Ser Leu Leu Lys
            500
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

12/48

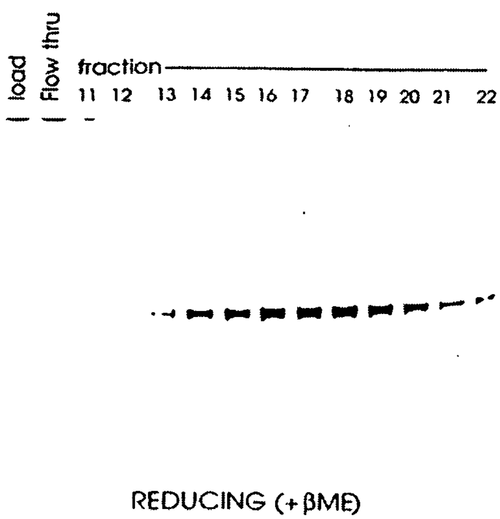


FIG. 6A

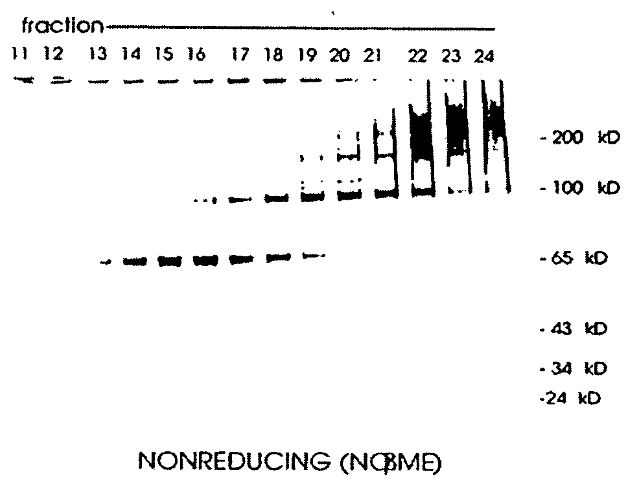
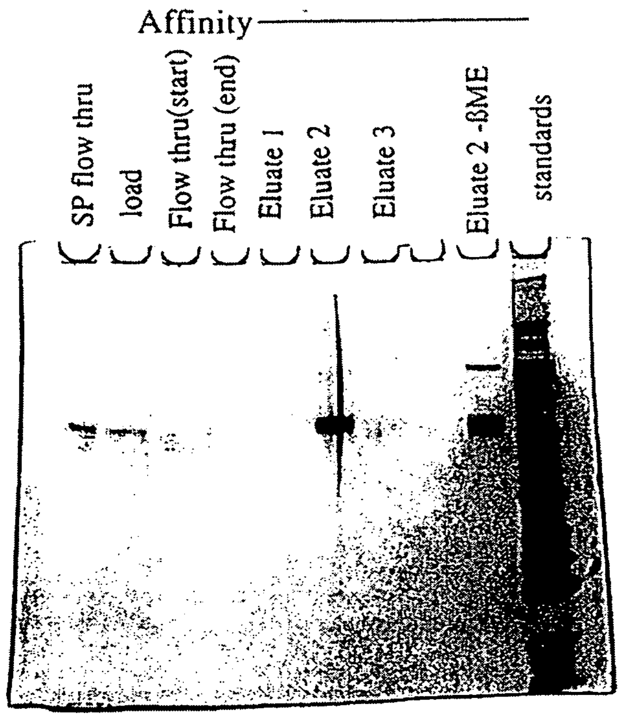


FIG. 6B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SP flow thru
load
Flow thru(start)
Flow thru (end)
Eluate 1
Eluate 2
Eluate 3
Eluate 2 -ßME
standards

FIG. 7

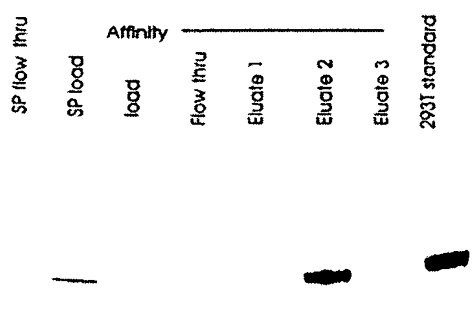
Affinity
SP flow thru
SP load
load
Flow thru
Eluate 1
Eluate 2
Eluate 3
293T standard

FIG. 8

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
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14/48

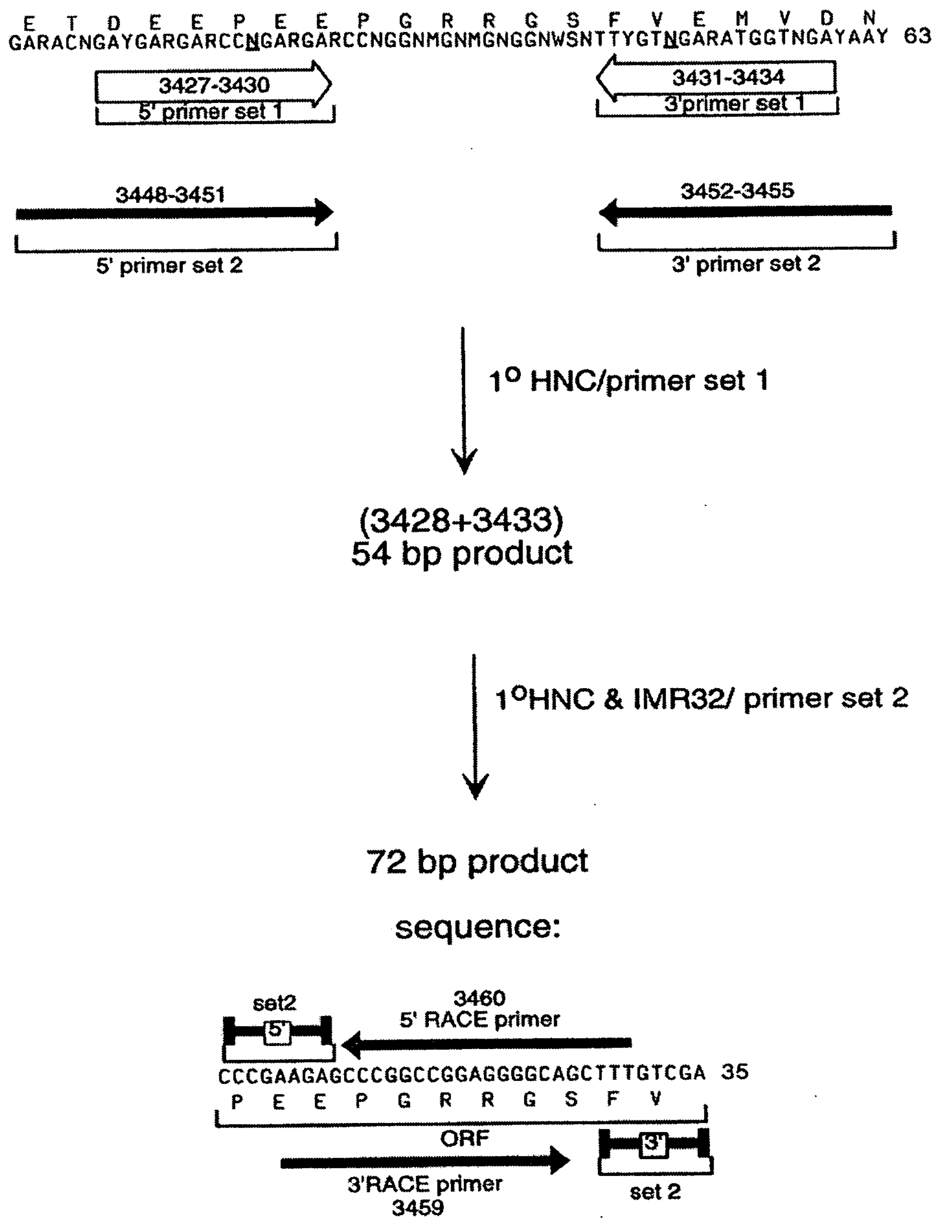

Fig. 9

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

15/48

```
                          10                  20                  30                  40
Hump501prot  M A Q A L P W L L L W M G A G V L P A H G T Q H G I R L P L R S G L G G A P L G  40
Musp501prot  M A P A L H W L L L W V G S G M L P A Q G T H L G I R L P L R S G L A G P P L G  40

                          50                  60                  70                  80
Hump501prot  L R L P R E T D E E P E E P G R R G S F V E M V D N L R G K S G Q G Y Y V E M T  80
Musp501prot  L R L P R E T D E E S E E P G R R G S F V E M V D N L R G K S G Q G Y Y V E M T  80

                          90                 100                 110                 120
Hump501prot  V G S P P Q T L N I L V D T G S S N F A V G A A P H P F L H R Y Y Q R Q L S S T  120
Musp501prot  V G S P P Q T L N I L V D T G S S N F A V G A A P H P F L H R Y Y Q R Q L S S T  120

                         130                 140                 150                 160
Hump501prot  Y R D L R K G V Y V P Y T Q G K W E G E L G T D L V S I P H G P N V T V R A N I  160
Musp501prot  Y R D L R K G V Y V P Y T Q G K W E G E L G T D L V S I P H G P N V T V R A N I  160

                         170                 180                 190                 200
Hump501prot  A A I T E S D K F F I N G S N W E G I L G L A Y A E I A R P D D S L E P F F D S  200
Musp501prot  A A I T E S D K F F I N G S N W E G I L G L A Y A E I A R P D D S L E P F F D S  200

                         210                 220                 230                 240
Hump501prot  L V K Q T H V P N L F S L Q L C G A G F P L N Q S E V L A S V G G S M I I G G I  240
Musp501prot  L V K Q T H I P N I F S L Q L C G A G F P L N Q T E A L A S V G G S M I I G G I  240

                         250                 260                 270                 280
Hump501prot  D H S L Y T G S L W Y T P I R R E W Y Y E V I I V R V E I N G Q D L K M D C K E  280
Musp501prot  D H S L Y T G S L W Y T P I R R E W Y Y E V I I V R V E I N G Q D L K M D C K E  280

                         290                 300                 310                 320
Hump501prot  Y N Y D K S I V D S G T T N L R L P K K V F E A A V K S I K A A S S T E K F P D  320
Musp501prot  Y N Y D K S I V D S G T T N L R L P K K V F E A A V K S I K A A S S T E K F P D  320

                         330                 340                 350                 360
Hump501prot  G F W L G E Q L V C W Q A G T T P W N I F P V I S L Y L M G E V T N Q S F R I T  360
Musp501prot  G F W L G E Q L V C W Q A G T T P W N I F P V I S L Y L M G E V T N Q S F R I T  360

                         370                 380                 390                 400
Hump501prot  I L P Q Q Y L R P V E D V A T S Q D D C Y K F A I S Q S S T G T V M G A V I M E  400
Musp501prot  I L P Q Q Y L R P V E D V A T S Q D D C Y K F A V S Q S S T G T V M G A V I M E  400

                         410                 420                 430                 440
Hump501prot  G F Y V V F D R A R K R I G F A V S A C H V H D E F R T A A V E G P F V T L D M  440
Musp501prot  G F Y V V F D R A R K R I G F A V S A C H V H D E F R T A A V E G P F V T A D M  440

                         450                 460                 470                 480
Hump501prot  E D C G Y N I P Q T D E S T L M T I A Y V M A A I C A L F M L P L C L M V C Q W  480
Musp501prot  E D C G Y N I P Q T D E S T L M T I A Y V M A A I C A L F M L P L C L M V C Q W  480

                         490                 500
Hump501prot  R C L R C L R Q Q H D D F A D D I S L L K                                        501
Musp501prot  R C L R C L R H Q H D D F G D D I S L L K                                        501
```

FIG. 10

CTGTTGGGCTCGCGGTTGAGGACAAACTCTTCGCGGTCTTTCCAGTACTCT
TGGATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCT
GAGCGAGTCCGCATCGACCGGATCGGAAAACCTCTCGACTGTTGGGGTGAG
TACTCCCTCTCAAAAGCGGGCATGACTTCTGCGCTAAGATTGTCAGTTTCC
AAAAACGAGGAGGATTTGATATTCACCTGGCCCGCGGTGATGCCTTTGAGG
GTGGCCGCGTCCATCTGGTCAGAAAAGACAATCTTTTTGTTGTCAAGCTTG
AGGTGTGGCAGGCTTGAGATCTGGCCATACACTTGAGTGACAATGACATCC
ACTTTGCCTTTCTCTCCACAGGTGTCCACTCCCAGGTCCAACTGCAGGTCG
ACTCTAGACCC

FIG. 11A

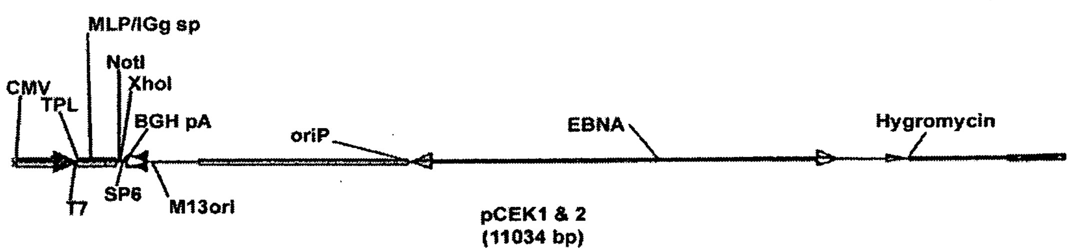

FIG. 11B

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

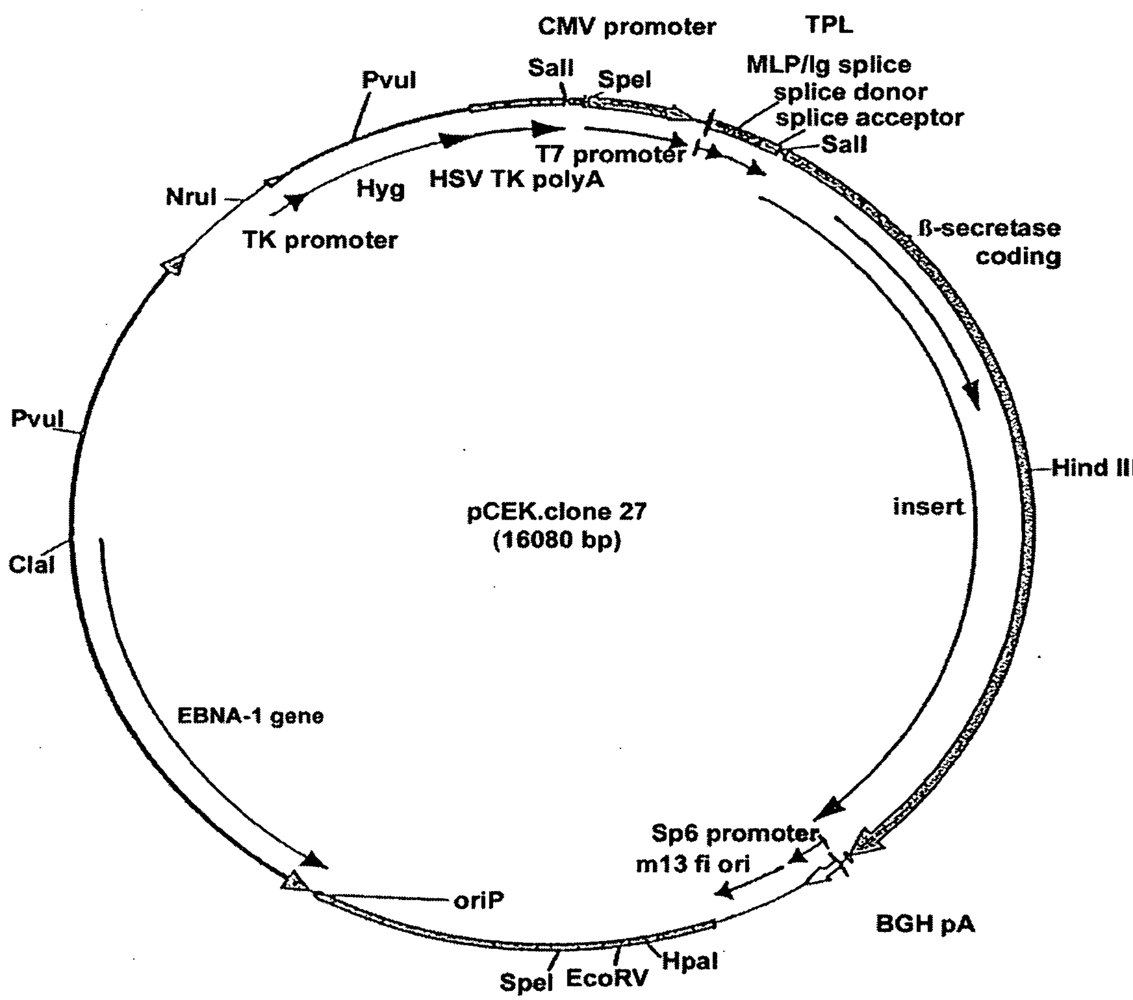

FIG. 12

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13A

```
ttctcatgtt tgacagctta tcatcgcaga tccgggcaac gttgttgcat tgctgcaggc 60

gcagaactgg taggtatgga agatccgatg tacgggccag atatacgcgt tgacattgat 120
     SpeI
tattgactag ttattaatag taatcaatta cggggtcatt agttcatagc ccatatatgg 180

agttccgcgt tacataactt acggtaaatg gcccgcctgg ctgaccgccc aacgaccccc 240

gcccattgac gtcaataatg acgtatgttc ccatagtaac gccaataggg actttccatt 300

gacgtcaatg ggtggactat ttacggtaaa ctgcccactt ggcagtacat caagtgtatc 360

atatgccaag tacgccccct attgacgtca atgacggtaa atggcccgcc tggcattatg 420

cccagtacat gaccttatgg gactttccta cttggcagta catctacgta ttagtcatcg 480

ctattaccat ggtgatgcgg ttttggcagt acatcaatgg gcgtggatag cggtttgact 540

cacggggatt tccaagtctc caccccattg acgtcaatgg gagtttgttt tggcaccaaa 600

atcaacggga ctttccaaaa tgtcgtaaca actccgcccc attgacgcaa atgggcggta 660

ggcgtgtacg gtgggaggtc tatataagca gagctctctg gctaactaga gaacccactg 720

cttactggct tatcgaaatt aatacgactc actataggga gacccaagct ctgttgggct 780
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13B

```
cgcggttgag gacaaactct tcgcggtctt tccagtactc ttggatcgga aacccgtcgg 840

cctccgaacg gtactccgcc accgagggac ctgagcgagt ccgcatcgac cggatcggaa 900
                      splice donor
aacctctcga ctgttggggt gagtactccc tctcaaaagc gggcatgact tctgcgctaa 960

gattgtcagt ttccaaaaac gaggaggatt tgatattcac ctggcccgcg gtgatgcctt 1020

tgagggtggc cgcgtccatc tggtcagaaa agacaatctt tttgttgtca agcttgaggt 1080

gtggcaggct tgagatctgg ccatacactt gagtgacaat gacatccact ttgcctttct 1140
     splice  acceptor                SalI
ctccacaggt gtccactccc aggtccaact gcaggtcgac tctagacccg gggaattctg 1200

cagatatcca tcacactggc cgcactcgtc cccagcccgc ccgggagctg cgagccgcga 1260

gctggattat ggtggcctga gcagccaacg cagccgcagg agcccggagc ccttgcccct 1320

gcccgcgccg ccgcccgccg gggggaccag ggaagccgcc accggcccgc catgcccgcc 1380

cctcccagcc ccgccgggag cccgcgcccg ctgcccaggc tggccgccgc cgtgccgatg 1440

tagcgggctc cggatcccag cctctcccct gctcccgtgc tctgcggatc tcccctgacc 1500

gctctccaca gcccggaccc gggggctggc ccagggccct gcaggccctg gcgtcctgat 1560

gcccccaagc tccctctcct gagaagccac cagcaccacc cagacttggg ggcaggcgcc 1620
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13C

```
agggacggac gtgggccagt gcgagcccag agggcccgaa ggccggggcc cacc atg   1677
                                                            Met
                                                              1

gcc caa gcc ctg ccc tgg ctc ctg ctg tgg atg ggc gcg gga gtg ctg   1725
Ala Gln Ala Leu Pro Trp Leu Leu Leu Trp Met Gly Ala Gly Val Leu
                5                  10                  15

cct gcc cac ggc acc cag cac ggc atc cgg ctg ccc ctg cgc agc ggc   1773
Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu Arg Ser Gly
         20                  25                  30

ctg ggg ggc gcc ccc ctg ggg ctg cgg ctg ccc cgg gag acc gac gaa   1821
Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu Thr Asp Glu
     35                  40                  45

gag ccc gag gag ccc ggc cgg agg ggc agc ttt gtg gag atg gtg gac   1869
Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu Met Val Asp
 50                  55                  60                  65

aac ctg agg ggc aag tcg ggg cag ggc tac tac gtg gag atg acc gtg   1917
Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu Met Thr Val
                70                  75                  80

ggc agc ccc ccg cag acg ctc aac atc ctg gtg gat aca ggc agc agt   1965
Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr Gly Ser Ser
            85                  90                  95
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13D

```
aac ttt gca gtg ggt gct gcc ccc cac ccc ttc ctg cat cgc tac tac    2013
Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His Arg Tyr Tyr
        100                 105                 110

cag agg cag ctg tcc agc aca tac cgg gac ctc cgg aag ggt gtg tat    2061
Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys Gly Val Tyr
    115                 120                 125

gtg ccc tac acc cag ggc aag tgg gaa ggg gag ctg ggc acc gac ctg    2109
Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly Thr Asp Leu
130                 135                 140                 145

gta agc atc ccc cat ggc ccc aac gtc act gtg cgt gcc aac att gct    2157
Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala Asn Ile Ala
                150                 155                 160

gcc atc act gaa tca gac aag ttc ttc atc aac ggc tcc aac tgg gaa    2205
Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser Asn Trp Glu
            165                 170                 175

ggc atc ctg ggg ctg gcc tat gct gag att gcc agg cct gac gac tcc    2253
Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro Asp Asp Ser
        180                 185                 190

ctg gag cct ttc ttt gac tct ctg gta aag cag acc cac gtt ccc aac    2301
Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His Val Pro Asn
    195                 200                 205
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13E

```
ctc ttc tcc ctg cag ctt tgt ggt gct ggc ttc ccc ctc aac cag tct     2349
Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu Asn Gln Ser
210                 215                 220                 225

gaa gtg ctg gcc tct gtc gga ggg agc atg atc att gga ggt atc gac     2397
Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly Gly Ile Asp
                230                 235                 240

cac tcg ctg tac aca ggc agt ctc tgg tat aca ccc atc cgg cgg gag     2445
His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile Arg Arg Glu
            245                 250                 255

tgg tat tat gag gtc atc att gtg cgg gtg gag atc aat gga cag gat     2493
Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn Gly Gln Asp
        260                 265                 270

ctg aaa atg gac tgc aag gag tac aac tat gac aag agc att gtg gac     2541
Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser Ile Val Asp
    275                 280                 285

agt ggc acc acc aac ctt cgt ttg ccc aag aaa gtg ttt gaa gct gca     2589
Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe Glu Ala Ala
290                 295                 300                 305

gtc aaa tcc atc aag gca gcc tcc tcc acg gag aag ttc cct gat ggt     2637
Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe Pro Asp Gly
                310                 315                 320
```

Figure 13F

```
ttc tgg cta gga gag cag ctg gtg tgc tgg caa gca ggc acc acc cct     2685
Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly Thr Thr Pro
            325                 330                 335

tgg aac att ttc cca gtc atc tca ctc tac cta atg ggt gag gtt acc     2733
Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly Glu Val Thr
        340                 345                 350

aac cag tcc ttc cgc atc acc atc ctt ccg cag caa tac ctg cgg cca     2781
Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr Leu Arg Pro
    355                 360                 365

gtg gaa gat gtg gcc acg tcc caa gac gac tgt tac aag ttt gcc atc     2829
Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys Phe Ala Ile
370                 375                 380                 385

tca cag tca tcc acg ggc act gtt atg gga gct gtt atc atg gag ggc     2877
Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile Met Glu Gly
                390                 395                 400

ttc tac gtt gtc ttt gat cgg gcc cga aaa cga att ggc ttt gct gtc     2925
Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly Phe Ala Val
            405                 410                 415

agc gct tgc cat gtg cac gat gag ttc agg acg gca gcg gtg gaa ggc     2973
Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala Val Glu Gly
        420                 425                 430
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13G

```
cct ttt gtc acc ttg gac atg gaa gac tgt ggc tac aac att cca cag    3021
Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn Ile Pro Gln
    435                 440                 445

aca gat gag tca acc ctc atg acc ata gcc tat gtc atg gct gcc atc    3069
Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met Ala Ala Ile
450                 455                 460                 465

tgc gcc ctc ttc atg ctg cca ctc tgc ctc atg gtg tgt cag tgg cgc    3117
Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys Gln Trp Arg
                470                 475                 480

tgc ctc cgc tgc ctg cgc cag cag cat gat gac ttt gct gat gac atc    3165
Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala Asp Asp Ile
            485                 490                 495

tcc ctg ctg aag tga ggaggcccat gggcagaaga tagagattcc cctggaccac    3220
Ser Leu Leu Lys
        500

acctccgtgg ttcactttgg tcacaagtag gagacacaga tggcacctgt ggccagagca 3280

cctcaggacc ctccccaccc accaaatgcc tctgccttga tggagaagga aaaggctggc 3340

aaggtgggtt ccagggactg tacctgtagg aaacagaaaa gagaagaaag aagcactctg 3400

ctggcgggaa tactcttggt cacctcaaat ttaagtcggg aaattctgct gcttgaaact 3460
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400
25/48

Figure 13H

tcagccctga acctttgtcc accattcctt taaattctcc aacccaaagt attcttcttt 3520

tcttagtttc agaagtactg gcatcacacg caggttacct tggcgtgtgt ccctgtggta 3580

HindIII

ccctggcaga gaagagacca agcttgtttc cctgctggcc aaagtcagta ggagaggatg 3640

cacagtttgc tatttgcttt agagacaggg actgtataaa caagcctaac attggtgcaa 3700

agattgcctc ttgaattaaa aaaaaaaact agattgacta tttatacaaa tgggggcggc 3760

tggaaagagg agaaggagag ggagtacaaa gacagggaat agtgggatca aagctaggaa 3820

aggcagaaac acaaccactc accagtccta gttttagacc tcatctccaa gatagcatcc 3880

catctcagaa gatgggtgtt gttttcaatg ttttcttttc tgtggttgca gcctgaccaa 3940

aagtgagatg ggaagggctt atctagccaa agagctcttt tttagctctc ttaaatgaag 4000

tgcccactaa gaagttccac ttaacacatg aatttctgcc atattaattt cattgtctct 4060

atctgaacca ccctttattc tacatatgat aggcagcact gaaatatcct aaccccctaa 4120

gctccaggtg ccctgtggga gagcaactgg actatagcag ggctgggctc tgtcttcctg 4180

gtcataggct cactctttcc cccaaatctt cctctggagc tttgcagcca aggtgctaaa 4240

aggaataggt aggagacctc ttctatctaa tccttaaaag cataatgttg aacattcatt 4300

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13I

caacagctga tgccctataa cccctgcctg gatttcttcc tattaggcta taagaagtag 4360

caagatcttt acataattca gagtggtttc attgccttcc taccctctct aatggcccct 4420

ccatttattt gactaaagca tcacacagtg gcactagcat tataccaaga gtatgagaaa 4480

tacagtgctt tatggctcta acattactgc cttcagtatc aaggctgcct ggagaaagga 4540

tggcagcctc agggcttcct tatgtcctcc accacaagag ctccttgatg aaggtcatct 4600

ttttccccta tcctgttctt cccctccccg ctcctaatgg tacgtgggta cccaggctgg 4660

ttcttgggct aggtagtggg gaccaagttc attacctccc tatcagttct agcatagtaa 4720

actacggtac cagtgttagt gggaagagct gggtttccct agtataccca ctgcatccta 4780

ctcctacctg gtcaacccgc tgcttccagg tatgggacct gctaagtgtg gaattacctg 4840

ataagggaga gggaaataca aggagggcct ctggtgttcc tggcctcagc cagctgccca 4900

caagccataa accaataaaa caagaatact gagtcagttt tttatctggg ttctcttcat 4960

tcccactgca cttggtgctg ctttggctga ctgggaacac cccataacta cagagtctga 5020

caggaagact ggagactgtc cacttctagc tcggaactta ctgtgtaaat aaactttcag 5080

aactgctacc atgaagtgaa aatgccacat tttgctttat aatttctacc catgttggga 5140

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

27/48

Figure 13J

aaaactggct ttttcccagc cctttccagg gcataaaact caaccccttc gatagcaagt 5200

cccatcagcc tattattttt ttaaagaaaa cttgcacttg tttttctttt tacagttact 5260

tccttcctgc cccaaaatta taaactctaa gtgtaaaaaa aagtcttaac aacagcttct 5320

tgcttgtaaa aatatgtatt atacatctgt atttttaaat tctgctcctg aaaaatgact 5380

gtcccattct ccactcactg catttggggc ctttcccatt ggtctgcatg tcttttatca 5440

ttgcaggcca gtggacagag ggagaaggga gaacaggggt cgccaacact tgtgttgctt 5500

tctgactgat cctgaacaag aaagagtaac actgaggcgc tcgctcccat gcacaactct 5560

ccaaaacact tatcctcctg caagagtggg ctttccgggt ctttactggg aagcagttaa 5620

gccccctcct caccccttcc ttttttcttt ctttactcct ttggcttcaa aggattttgg 5680

aaaagaaaca atatgcttta cactcatttt caatttctaa atttgcaggg gatactgaaa 5740

aatacggcag gtggcctaag gctgctgtaa agttgagggg agaggaaatc ttaagattac 5800

aagataaaaa acgaatcccc taaacaaaaa gaacaataga actggtcttc cattttgcca 5860

cctttcctgt tcatgacagc tactaacctg gagacagtaa catttcatta accaaagaaa 5920

gtgggtcacc tgacctctga agagctgagt actcaggcca ctccaatcac cctacaagat 5980

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13K

gccaaggagg tcccaggaag tccagctcct taaactgacg ctagtcaata aacctgggca 6040

agtgaggcaa gagaaatgag gaagaatcca tctgtgaggt gacaggcacg gatgaaagac 6100

aaagacggaa aagagtatca aaggcagaaa ggagatcatt tagttgggtc tgaaaggaaa 6160

agtntttgct atccgacatg tactgctagt wcctgtaagc attttaggtc ccagaatgga 6220

aaaaaaaatc aagctatngg ttatataata atgnnnnnnn nnnnnnnnnn nntcgagcat 6280

gcatctagag ggccctattc tatagtgtca cctaaatgct agagctcgct gatcagcctc 6340

gactgtgcct tctagttgcc agccatctgt tgtttgcccc tcccccgtgc cttccttgac 6400

cctggaaggt gccactccca ctgtcctttc ctaataaaat gaggaaattg catcgcattg 6460

tctgagtagg tgtcattcta ttctgggggg tggggtgggg caggacagca agggggagga 6520

ttgggaagac aatagcaggc atgctgggga tgcggtgggc tctatggctt ctgaggcgga 6580

aagaaccagc tggggctcta gggggtatcc ccacgcgccc tgtagcggcg cattaagcgc 6640

ggcgggtgtg gtggttacgc gcagcgtgac cgctacactt gccagcgccc tagcgcccgc 6700

tcctttcgct ttcttccctt cctttctcgc cacgttcgcc ggctttcccc gtcaagctct 6760

aaatcggggc atccctttag ggttccgatt tagtgcttta cggcacctcg accccaaaaa 6820

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13L

```
acttgattag ggtgatggtt cacgtagtgg gccatcgccc tgatagacgg tttttcgccc 6880

tttgacgttg gagtccacgt tctttaatag tggactcttg ttccaaactg gaacaacact 6940

caaccctatc tcggtctatt cttttgattt ataagggatt ttggggattt cggcctattg 7000

gttaaaaaat gagctgattt aacaaaaatt taacgcgaat tctagagccc cgccgccgga 7060

cgaactaaac ctgactacgg catctctgcc ccttcttcgc ggggcagtgc atgtaatccc 7120

ttcagttggt tggtacaact tgccaactgg gccctgttcc acatgtgaca cgggggggga 7180

ccaaacacaa aggggttctc tgactgtagt tgacatcctt ataaatggat gtgcacattt 7240

gccaacactg agtggctttc atcctggagc agactttgca gtctgtggac tgcaacacaa 7300

cattgccttt atgtgtaact cttggctgaa gctcttacac caatgctggg ggacatgtac 7360

ctcccagggg cccaggaaga ctacgggagg ctacaccaac gtcaatcaga ggggcctgtg 7420

tagctaccga taagcggacc ctcaagaggg cattagcaat agtgtttata aggcccccttt 7480
HpaI
gttaacccta aacgggtagc atatgcttcc cgggtagtag tatatactat ccagactaac 7540

cctaattcaa tagcatatgt tacccaacgg gaagcatatg ctatcgaatt agggttagta 7600
                      EcoRV
aaagggtcct aaggaacagc gatatctccc accccatgag ctgtcacggt tttatttaca 7660
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13M

```
tggggtcagg attccacgag ggtagtgaac cattttagtc acaagggcag tggctgaaga 7720

tcaaggagcg ggcagtgaac tctcctgaat cttcgcctgc ttcttcattc tccttcgttt 7780

agctaataga ataactgctg agttgtgaac agtaaggtgt atgtgaggtg ctcgaaaaca 7840

aggtttcagg tgacgccccc agaataaaat ttggacgggg ggttcagtgg tggcattgtg 7900
                                                SpeI
ctatgacacc aatataaccc tcacaaaccc cttgggcaat aaatactagt gtaggaatga 7960

aacattctga atatctttaa caatagaaat ccatggggtg gggacaagcc gtaaagactg 8020

gatgtccatc tcacacgaat ttatggctat gggcaacaca taatcctagt gcaatatgat 8080

actggggtta ttaagatgtg tcccaggcag ggaccaagac aggtgaacca tgttgttaca 8140

ctctatttgt aacaagggga aagagagtgg acgccgacag cagcggactc cactggttgt 8200

ctctaacacc cccgaaaatt aaacggggct ccacgccaat ggggcccata aacaaagaca 8260

agtggccact cttttttttg aaattgtgga gtgggggcac gcgtcagccc ccacacgccg 8320

ccctgcggtt ttggactgta aaataagggt gtaataactt ggctgattgt aaccccgcta 8380

accactgcgg tcaaaccact tgcccacaaa accactaatg gcaccccggg gaatacctgc 8440

ataagtaggt gggcgggcca agataggggc gcgattgctg cgatctggag gacaaattac 8500
```

Figure 13N

```
acacacttgc gcctgagcgc caagcacagg gttgttggtc ctcatattca cgaggtcgct 8560

gagagcacgg tgggctaatg ttgccatggg tagcatatac tacccaaata tctggatagc 8620

atatgctatc ctaatctata tctgggtagc ataggctatc ctaatctata tctgggtagc 8680

atatgctatc ctaatctata tctgggtagt atatgctatc ctaatttata tctgggtagc 8740

ataggctatc ctaatctata tctgggtagc atatgctatc ctaatctata tctgggtagt 8800

atatgctatc ctaatctgta tccgggtagc atatgctatc ctaatagaga ttagggtagt 8860

atatgctatc ctaatttata tctgggtagc atatactacc caaatatctg gatagcatat 8920

gctatcctaa tctatatctg ggtagcatat gctatcctaa tctatatctg ggtagcatag 8980

gctatcctaa tctatatctg ggtagcatat gctatcctaa tctatatctg ggtagtatat 9040

gctatcctaa tttatatctg ggtagcatag gctatcctaa tctatatctg ggtagcatat 9100

gctatcctaa tctatatctg ggtagtatat gctatcctaa tctgtatccg ggtagcatat 9160

gctatcctca tgcatataca gtcagcatat gatacccagt agtagagtgg gagtgctatc 9220

ctttgcatat gccgccacct cccaaggggg cgtgaatttt cgctgcttgt ccttttcctg 9280
     oriP
catgctggtt gctcccattc ttaggtgaat ttaaggaggc caggctaaag ccgtcgcatg 9340
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 130

tctgattgct caccaggtaa atgtcgctaa tgttttccaa cgcgagaagg tgttgagcgc 9400

ggagctgagt gacgtgacaa catgggtatg cccaattgcc ccatgttggg aggacgaaaa 9460

tggtgacaag acagatggcc agaaatacac caacagcacg catgatgtct actggggatt 9520

tattctttag tgcgggggaa tacacggctt ttaatacgat tgagggcgtc tcctaacaag 9580

ttacatcact cctgcccttc ctcaccctca tctccatcac ctccttcatc tccgtcatct 9640

ccgtcatcac cctccgcggc agccccttcc accataggtg gaaaccaggg aggcaaatct 9700

actccatcgt caaagctgca cacagtcacc ctgatattgc aggtaggagc gggctttgtc 9760

ataacaaggt ccttaatcgc atccttcaaa acctcagcaa atatatgagt ttgtaaaaag 9820

accatgaaat aacagacaat ggactccctt agcgggccag gttgtgggcc gggtccaggg 9880

gccattccaa aggggagacg actcaatggt gtaagacgac attgtggaat agcaagggca 9940

gttcctcgcc ttaggttgta aagggaggtc ttactacctc catatacgaa cacaccggcg 10000

acccaagttc cttcgtcggt agtcctttct acgtgactcc tagccaggag agctcttaaa 10060

ccttctgcaa tgttctcaaa tttcgggttg gaacctcctt gaccacgatg ctttccaaac 10120

caccctcctt ttttgcgcct gcctccatca ccctgacccc ggggtccagt gcttgggcct 10180

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13P

tctcctgggt catctgcggg gccctgctct atcgctcccg ggggcacgtc aggctcacca 10240

tctgggccac cttcttggtg gtattcaaaa taatcggctt cccctacagg gtggaaaaat 10300

ggccttctac ctggaggggg cctgcgcggt ggagacccgg atgatgatga ctgactactg 10360

ggactcctgg gcctcttttc tccacgtcca cgacctctcc ccctggctct ttcacgactt 10420

ccccccctgg ctctttcacg tcctctaccc cggcggcctc cactacctcc tcgaccccgg 10480

cctccactac ctcctcgacc ccggcctcca ctgcctcctc gaccccggcc tccacctcct 10540

gctcctgccc ctcctgctcc tgcccctcct cctgctcctg cccctcctgc ccctcctgct 10600

cctgcccctc ctgcccctcc tgctcctgcc cctcctgccc ctcctgctcc tgcccctcct 10660

gcccctcctc ctgctcctgc ccctcctgcc cctcctcctg ctcctgcccc tcctgcccct 10720

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gctcctgccc ctcctcctgc tcctgcccct cctgcccctc ctgcccctcc tcctgctcct 10960

gcccctcctg cccctcctcc tgctcctgcc cctcctcctg ctcctgcccc tcctgcccct 11020

34/48

Figure 13Q

cctgcccctc ctcctgctcc tgcccctcct gcccctcctc ctgctcctgc ccctcctcct 11080

gctcctgccc ctcctgcccc tcctgcccct cctcctgctc ctgcccctcc tcctgctcct 11140

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cctgcccctc ctgctcctgc ccctcccgct cctgctcctg ctcctgttcc accgtgggtc 11260

cctttgcagc caatgcaact tggacgtttt tggggtctcc ggacaccatc tctatgtctt 11320

ggccctgatc ctgagccgcc cggggctcct ggtcttccgc ctcctcgtcc tcgtcctctt 11380

ccccgtcctc gtccatggtt atcacccct cttctttgag gtccactgcc gccggagcct 11440

tctggtccag atgtgtctcc cttctctcct aggccatttc caggtcctgt acctggcccc 11500

tcgtcagaca tgattcacac taaaagagat caatagacat ctttattaga cgacgctcag 11560

tgaatacagg gagtgcagac tcctgccccc tccaacagcc cccccaccct catccccttc 11620

atggtcgctg tcagacagat ccaggtctga aaattcccca tcctccgaac catcctcgtc 11680

ctcatcacca attactcgca gcccggaaaa ctcccgctga acatcctcaa gatttgcgtc 11740

ctgagcctca agccaggcct caaattcctc gtcccccttt ttgctggacg gtagggatgg 11800

ggattctcgg gacccctcct cttcctcttc aaggtcacca gacagagatg ctactggggc 11860

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400
35/48

Figure 13R

```
                                                ClaI
aacggaagaa aagctgggtg cggcctgtga ggatcagctt atcgatgata agctgtcaaa 11920

catgagaatt cttgaagacg aaagggcctc gtgatacgcc tatttttata ggttaatgtc 11980

atgataataa tggtttctta gacgtcaggt ggcacttttc ggggaaatgt gcgcggaacc 12040

cctatttgtt tatttttcta aatacattca aatatgtatc cgctcatgag acaataaccc 12100

tgataaatgc ttcaataata ttgaaaaagg aagagtatga gtattcaaca tttccgtgtc 12160

gcccttattc ccttttttgc ggcattttgc cttcctgttt ttgctcaccc agaaacgctg 12220

gtgaaagtaa aagatgctga agatcagttg ggtgcacgag tgggttacat cgaactggat 12280

ctcaacagcg gtaagatcct tgagagtttt cgccccgaag aacgttttcc aatgatgagc 12340

acttttaaag ttctgctatg tggcgcggta ttatcccgtg ttgacgccgg gcaagagcaa 12400

ctcggtcgcc gcatacacta ttctcagaat gacttggttg agtactcacc agtcacagaa 12460

aagcatctta cggatggcat gacagtaaga gaattatgca gtgctgccat aaccatgagt 12520
                                 PvuI
gataacactg cggccaactt acttctgaca acgatcggag gaccgaagga gctaaccgct 12580

tttttgcaca acatggggga tcatgtaact cgccttgatc gttgggaacc ggagctgaat 12640

gaagccatac caaacgacga gcgtgacacc acgatgcctg cagcaatggc aacaacgttg 12700
```

36/48

Figure 13S

cgcaaactat taactggcga actacttact ctagcttccc ggcaacaatt aatagactgg 12760

atggaggcgg ataaagttgc aggaccactt ctgcgctcgg cccttccggc tggctggttt 12820

attgctgata aatctggagc cggtgagcgt gggtctcgcg gtatcattgc agcactgggg 12880

ccagatggta agccctcccg tatcgtagtt atctacacga cggggagtca ggcaactatg 12940

gatgaacgaa atagacagat cgctgagata ggtgcctcac tgattaagca ttggtaactg 13000

tcagaccaag tttactcata tatactttag attgatttaa aacttcattt ttaatttaaa 13060

aggatctagg tgaagatcct ttttgataat ctcatgacca aaatccctta acgtgagttt 13120

tcgttccact gagcgtcaga ccccgtagaa aagatcaaag gatcttcttg agatcctttt 13180

tttctgcgcg taatctgctg cttgcaaaca aaaaaaccac cgctaccagc ggtggtttgt 13240

ttgccggatc aagagctacc aactcttttt ccgaaggtaa ctggcttcag cagagcgcag 13300

ataccaaata ctgtccttct agtgtagccg tagttaggcc accacttcaa gaactctgta 13360

gcaccgccta catacctcgc tctgctaatc ctgttaccag tggctgctgc cagtggcgat 13420

aagtcgtgtc ttaccgggtt ggactcaaga cgatagttac cggataaggc gcagcggtcg 13480

ggctgaacgg ggggttcgtg cacacagccc agcttggagc gaacgaccta caccgaactg 13540

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13T

```
agatacctac agcgtgagct atgagaaagc gccacgcttc ccgaagggag aaaggcggac 13600

aggtatccgg taagcggcag ggtcggaaca ggagagcgca cgagggagct tccaggggga 13660

aacgcctggt atctttatag tcctgtcggg tttcgccacc tctgacttga gcgtcgattt 13720

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ttcttggagt ggtgaatccg ttagcgaggt gccgccggct tccattcagg tcgaggtggc 13960

ccggctccat gcaccgcgac gcaacgcggg gaggcagaca aggtataggg cggcgcctac 14020

aatccatgcc aacccgttcc atgtgctcgc cgaggcggca taaatcgccg tgacgatcag 14080

cggtccagtg atcgaagtta ggctggtaag agccgcgagc gatccttgaa gctgtccctg 14140

atggtcgtca tctacctgcc tggacagcat ggcctgcaac gcgggcatcc cgatgccgcc 14200
                                                  NruI
ggaagcgaga agaatcataa tggggaaggc catccagcct cgcgtcgcga acgccagcaa 14260

gacgtagccc agcgcgtcgg ccgccatgcc ctgcttcatc cccgtggccc gttgctcgcg 14320

tttgctggcg gtgtccccgg aagaaatata tttgcatgtc tttagttcta tgatgacaca 14380
```

Figure 13U

aaccccgccc agcgtcttgt cattggcgaa ttcgaacacg cagatgcagt cggggcggcg 14440

cggtcccagg tccacttcgc atattaaggt gacgcgtgtg gcctcgaaca ccgagcgacc 14500

ctgcagcgac ccgcttaaca gcgtcaacag cgtgccgcag atcccgggca atgagatatg 14560

aaaaagcctg aactcaccgc gacgtctgtc gagaagtttc tgatcgaaaa gttcgacagc 14620

gtctccgacc tgatgcagct ctcggagggc gaagaatctc gtgctttcag cttcgatgta 14680

ggagggcgtg gatatgtcct gcgggtaaat agctgcgccg atggtttcta caaagatcgt 14740

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ggaattcagc gagagcctga cctattgcat ctcccgccgt gcacagggtg tcacgttgca 14860

agacctgcct gaaaccgaac tgcccgctgt tctgcagccg gtcgcggagg ccatggatgc 14920

PvuI

gatcgctgcg gccgatctta gccagacgag cgggttcggc ccattcggac cgcaaggaat 14980

cggtcaatac actacatggc gtgatttcat atgcgcgatt gctgatcccc atgtgtatca 15040

ctggcaaact gtgatggacg acaccgtcag tgcgtccgtc gcgcaggctc tcgatgagct 15100

gatgctttgg gccgaggact gccccgaagt ccggcacctc gtgcacgcgg atttcggctc 15160

caacaatgtc ctgacggaca atggccgcat aacagcggtc attgactgga gcgaggcgat 15220

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

Figure 13V

```
gttcggggat tcccaatacg aggtcgccaa catcttcttc tggaggccgt ggttggcggg 15280

tatggagcag cagacgcgct acttcgagcg gaggcatccg gagcttgcag gatcgccgcg 15340

gctccgggcg tatatgctcc gcattggtct tgaccaactc tatcagagct tggttgacgg 15400

caatttcgat gatgcagctt gggcgcaggg tcgatgcgac gcaatcgtcc gatccggagc 15460

cgggactgtc gggcgtacac aaatcgcccg cagaagcgcg gccgtctgga ccgatggctg 15520

tgtagaagta ctcgccgata gtggaaacgg gagatggggg aggctaactg aaacacggaa 15580

ggagacaata ccggaaggaa cccgcgctat gacggcaata aaaagacaga ataaaacgca 15640

cgggtgttgg gtcgtttgtt cataaacgcg gggttcggtc ccagggctgg cactctgtcg 15700

ataccccacc gagaccccat tggggccaat acgcccgcgt ttcttccttt tccccacccc 15760

acccccccaag ttcgggtgaa ggcccagggc tcgcagccaa cgtcggggcg gcaggccctg 15820

ccatagccac tggccccgtg ggttagggac ggggtccccc atggggaatg gtttatggtt 15880

cgtgggggtt attattttgg gcgttgcgtg gggtctggtc cacgactgga ctgagcagac 15940

agacccatgg tttttggatg gcctgggcat ggaccgcatg tactggcgcg acacgaacac 16000

cgggcgtctg tggctgccaa acacccccga cccccaaaaa ccaccgcgcg gatttctggc 16060
```

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

40/48

Figure 13W

```
          SalI
gtgccaagct agtcgaccaa    16080
▲
```

CTGTTGGGCTCGCGGTTGAGGACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAAC
CCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGAT
CGGAAAACCTCTCGACTGTTGGGGTGAGTACTCCCTCTCAAAAGCGGGCATGACTTCTGCGCT
AAGATTGTCAGTTTCCAAAAACGAGGAGGATTTGATATTCACCTGGCCCGCGGTGATGCCTTT
GAGGGTGGCCGCGTCCATCTGGTCAGAAAAGACAATCTTTTTGTTGTCAAGCTTGAGGTGTGG
CAGGCTTGAGATCTGGCCATACACTTGAGTGACAATGACATCCACTTTGCCTTTCTCTCCACAG
GTGTCCACTCCCAGGTCCAACTGCAGGTCGACTCTAGACCC

FIG. 14A

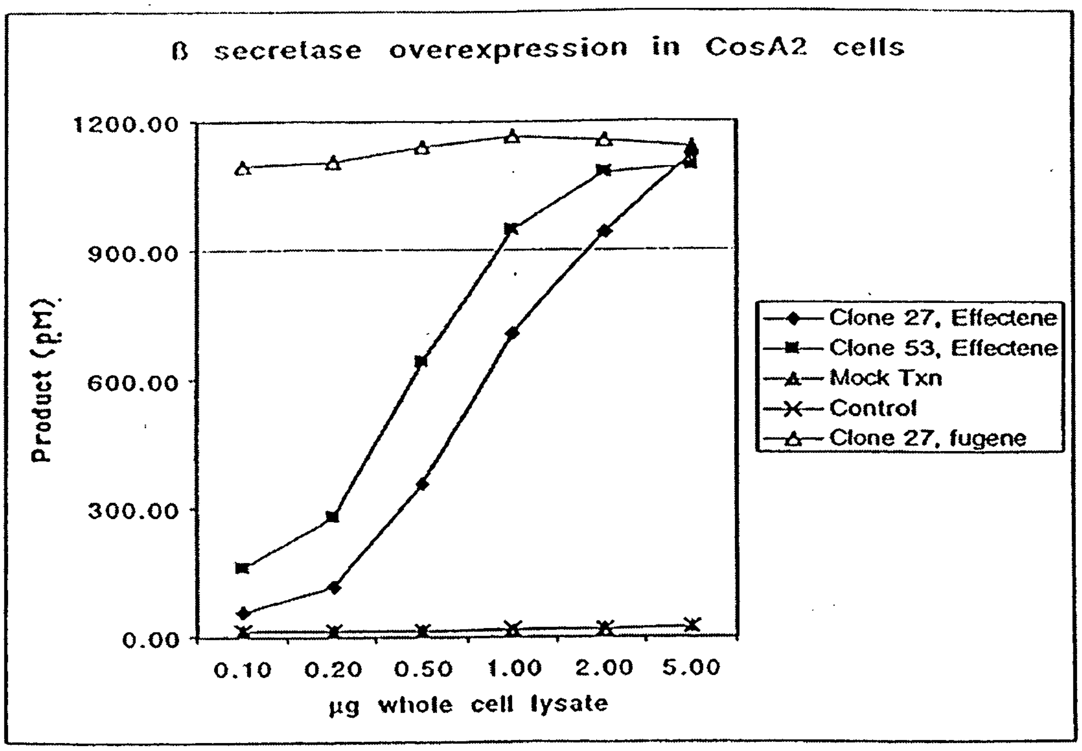

FIG. 14B

John P. Anderson, *et al.* Application No. 09/724,569
"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

42/48

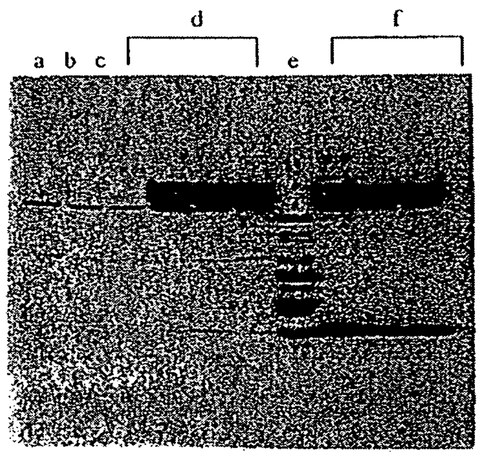

FIG. 15A

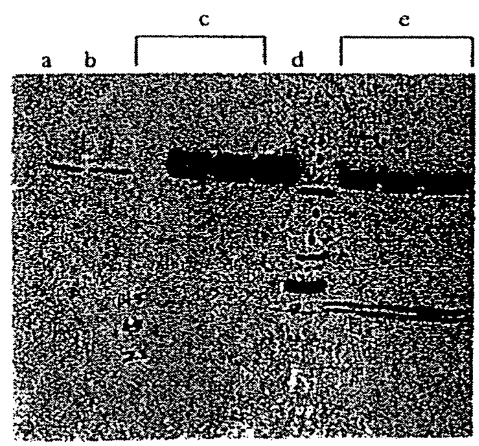

FIG. 15B

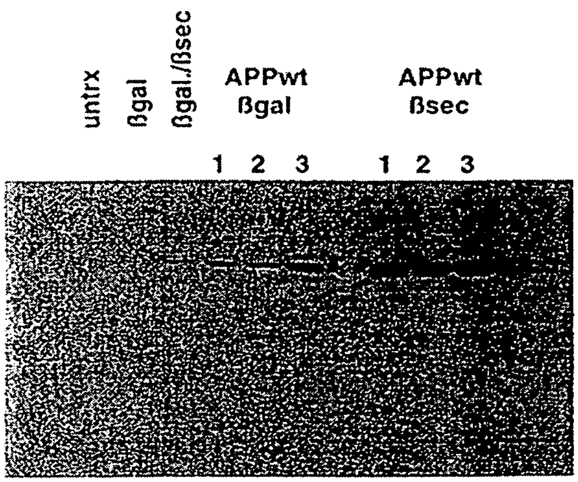

FIG. 16A

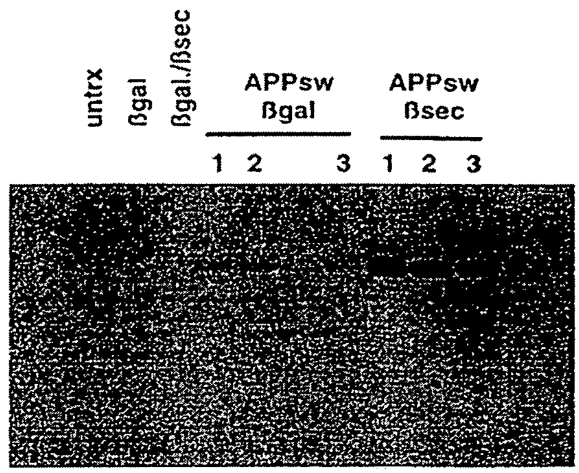

FIG. 16B

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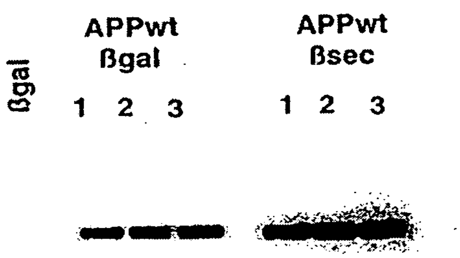

FIG. 17A

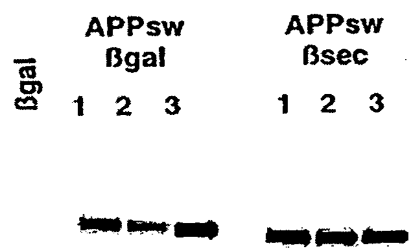

FIG. 17B

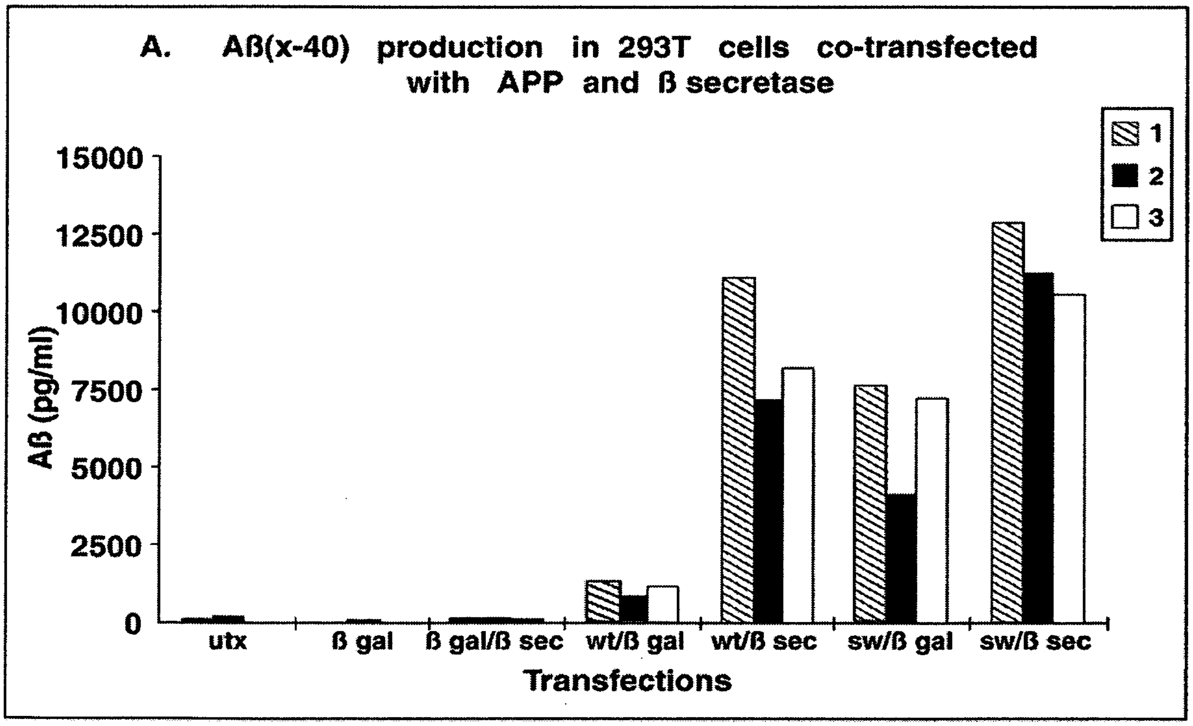
A. Aß(x-40) production in 293T cells co-transfected with APP and ß secretase
1
2
3
15000
12500
10000
7500
5000
2500
0
Aß (pg/ml)
utx
ß gal
ß gal/ß sec
wt/ß gal
wt/ß sec
sw/ß gal
sw/ß sec
Transfections

Fig. 18

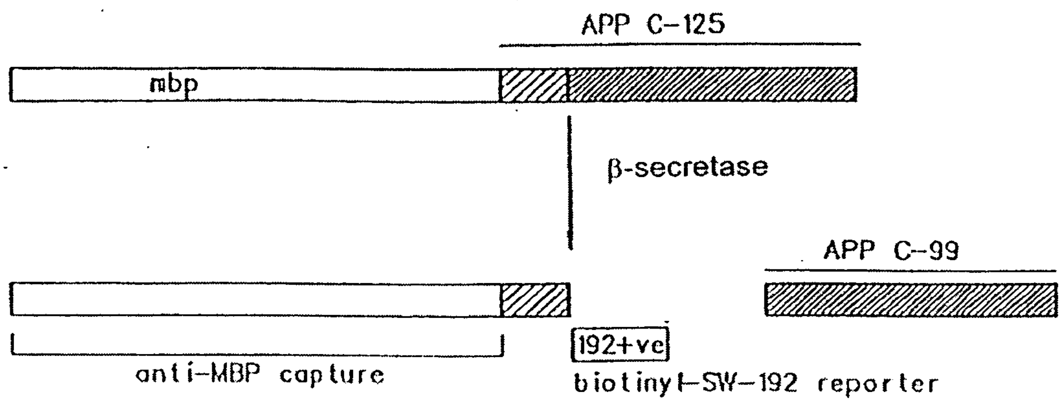

FIG. 19A

Wild-Type Sequence	....Val-Lys-Met-Asp...
Swedish Sequence	....Val-Asn-Leu-Asp...

FIG. 19B

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"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

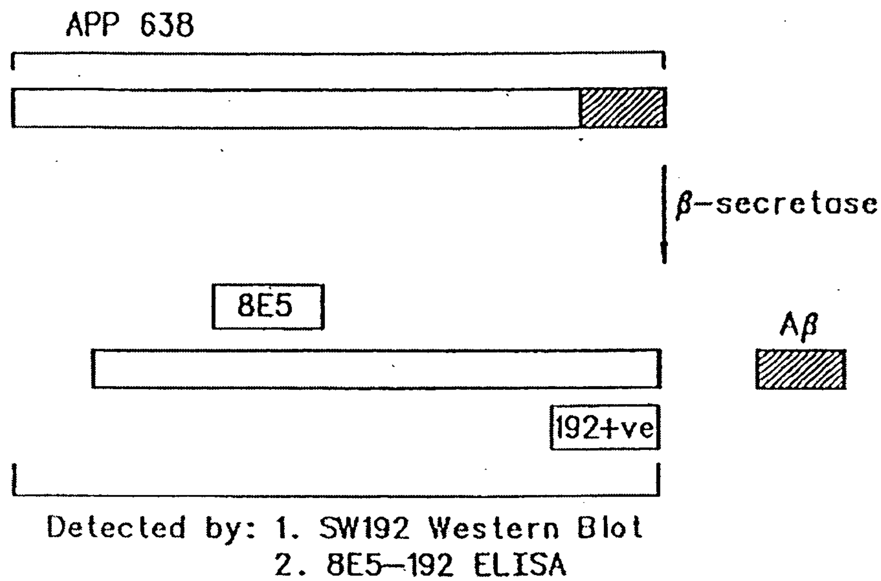

FIG. 20

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"Beta-Secretase Enzyme Compositions and Methods"
Attorney Docket No. 015270-006446US
Joe Liebeschuetz, Reg. No. 37,505 (650) 326-2400

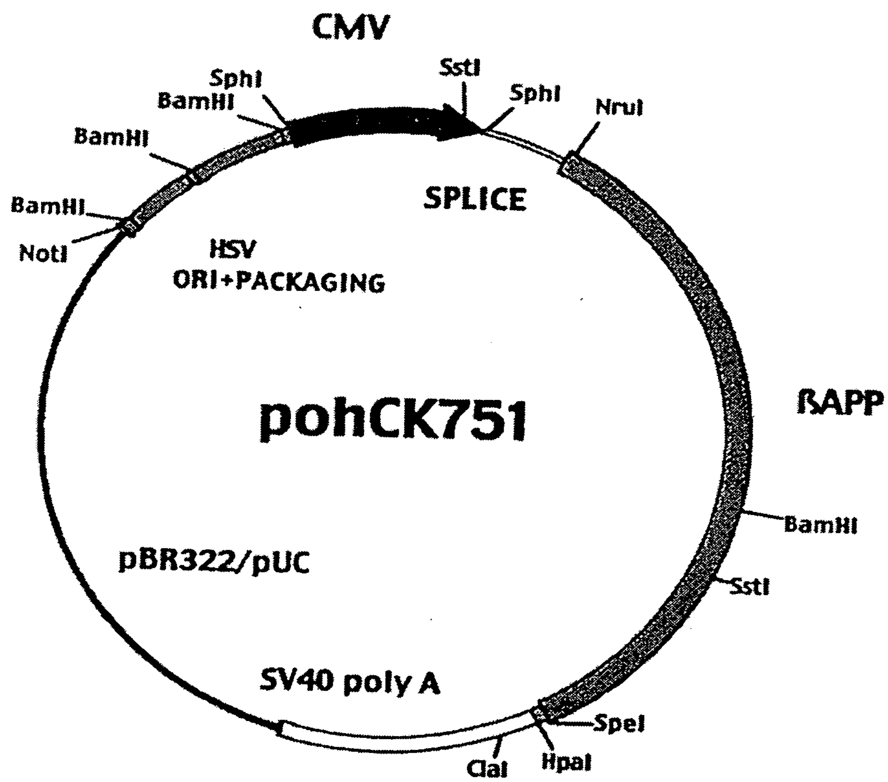

FIG. 21